HFD-613/DGD

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Servic_e_

Food and Drug Administration
Rockville MD 20857

NDA 11-839/S-068

Pharmacia & Upjohn
Attention: Donald R. Gieseker, Pharm. D.
Associate Director, Regulatory Affairs
7000 Portage Road
Kalamazoo, MI 4900 1-0199

AUG 0 4 1998

Dear Dr. Gieseker:

Please refer to your supplemental new drug application dated July 3 1, 1997, received August 4, 1997, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Provera (medroxyprogesterone acetate) 5mg and 10mg tablets.

We acknowledge receipt of your submissions dated September 2, 1997, and January 8, June 29, July 22 and August 3, 1998. The user fee goal date for this application is August 4, 1998.

This supplemental new drug application provides for the use of Provera for the reduction of endometrial hyperplasia in postmenopausal women receiving 0.625mg conjugated estrogens for 12 to 14 consecutive days per month, either beginning on the 1 st day of the cycle or the 16th day of the cycle.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert and container and carton labels dated August 3, 1998). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 11-839/S-068." Approval of this submission by FDA is not required before the labeling is used.

If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional materials that you propose

to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Healthcare Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact John C. Markow, Project Manager, at (301) 827-4260.

Sincerely,

8/4/98

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Provera®

medroxyprogesterone acetate tablets, USP

Pharmacia &Upjohn

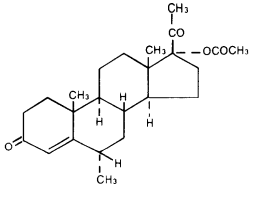
Provera brand of medroxyprogesterone acetate tablets

0812584512

DESCRIPTION

PROVERA Tablets contain medroxyprogesterone acetate, which is a derivative of progesterone. It is a white to off-white, odorless crystalline powder, stable in air, melting between 200 and 210°C. It is freely soluble in chloroform, soluble in acetone and in dioxane, sparingly soluble in alcohol and in methanol, slightly soluble in ether, and insoluble in water.

The chemical name for medroxyprogesterone acetate is Pregn-4-ene-3,20-dione, 17-(acetyloxy)-6-methyl-, (6a)-. The structural formula is:



Each PROVERA tablet for oral administration contains 2.5 mg, 5 mg or 10 mg of medroxyprogesterone acetate. Inactive ingredients: calcium stearate, corn starch, lactose, mineral oil, sorbic acid, sucrose, talc. The 2.5 mg tablet contains FD&C Yellow no. 6.

CLINICAL PHARMACOLOGY

Medroxyprogesterone acetate (MPA), administered orally or parenterally in the recommended doses to women with adequate endogenous estrogen, transforms proliferative into secretory endometrium. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant estrogenic activity. While parenterally administered MPA inhibits gonadotropin production, which in turn prevents follicular maturation and ovulation, available data indicate that this does not occur when the usually recommended oral dosage is given as single daily doses.

Pharmacokinetics

The pharmacokinetics of MPA were determined in 20 postmenopausal women following a single-dose administration of eight PROVERA Tablets 2.5 mg or a single administration of two PROVERA Tablets 10 mg under fasting conditions. In another study, the steady-state pharmacokinetics of MPA were determined under fasting conditions in 30 postmenopausal women following daily administration of one PROVERA Tablet 10 mg for 7 days. In both studies, MPA was quantitated in serum using a validated gas chromatography-mass spectrometry (GC-MS) method. Estimates of the pharmacokinetic parameters of MPA after single and multiple doses of PROVERA Tablets were highly variable and are summarized in Table 1.

Table 1. Mean (SD) Pharmacokinetic Parameters for Medroxyprogesterone Acetate (MPA)

Tablet Strength	C_{max} (ng/mL)	T_{max} (h)	$Auc_{0-\infty}$ (ng*h/mL)	$t_{1/2}$ (h)	Vd/f (L)	CL/f (mL/min)
Single Dose						
2 x 10 mg	1.01 (0.599)	2.65 (1.41)	6.95 (3.39)	12.1 (3.49)	78024 (47220)	64110 (42662)
8 x 2.5 mg	0.805 (0.413)	2.22 (1.39)	5.62 (2.79)	11.6 (2.81)	62748 (40146)	74123 (35126)
Multiple Dose						
10 mg*	0.71 (0.35)	2.83 (1.83)	6.01 (3.16)	16.6 (15.0)	40564 (38256)	41963 (38402)

*Following Day 7 dose

Absorption: *No* specific investigation on the absolute bioavailability of MPA in humans has been conducted. MPA is rapidly absorbed from the gastrointestinal tract, and maximum MPA concentrations are obtained between 2 to 4 hours after oral administration.

Effect of Food: Administration of PROVERA with food increases the bioavailability of MPA. A 10-mg dose of PROVERA, taken immediately before or after a meal, increased MPA C_{max} (50 to 70%) and AUC (18 to 33%). The half-life of MPA was not changed with food.

Distribution: MPA is approximately 90% protein bound, primarily to albumin; no MPA binding occurs with sex-hormone binding globulin. The unbound MPA modulates pharmacologic responses.

Metabolism: Following oral dosing, MPA is extensively metabolized in the liver via ring A and/or side-chain hydroxylation, with subsequent conjugation and elimination in the urine. At least 16 MPA metabolites have been identified.

Excretion: Most MPA metabolites are excreted in the urine as glucuronide conjugates with only minor amounts excreted as sulfates. Mean percent dose excreted in the 24-hour urine of patients with fatty liver as intact MPA after a 10-mg or 100-mg dose was 7.3% and 6.4%, respectively.

Special Populations

Renal Insufficiency: The pharmacokinetics of MPA in patients with varying degrees of renal insufficiency have not been investigated. The renal clearance of MPA is negligible and a decrease in total body clearance is not expected in patients with renal insufficiency.

Hepatic Insufficiency: MPA is almost exclusively eliminated via hepatic metabolism. In 14 patients with advanced liver disease, MPA disposition was significantly altered (reduced elimination). As such, PROVERA is contraindicated in patients with severe hepatic disease (see CONTRAINDICATIONS). However, for patients with mild-moderate degree of hepatic impairment, a lower dose of PROVERA or a less frequent administration should be considered.

Drug-Drug Interactions

No formal pharmacokinetic drug-drug interaction studies have been conducted with PROVERA. However, published literature indicates that coadministration of conjugated estrogens with MPA does not affect the pharmacokinetic profile of MPA; similarly, MPA does not affect the pharmacokinetic profile of the conjugated or unconjugated estrogens. Literature data also indicate that concomitant administration with aminoglutethimide would significantly reduce serum concentrations of MPA, likely by increasing the clearance of the drug.

CLINICAL STUDIES

The use of unopposed estrogen therapy has been associated with an increased risk of endometrial hyperplasia, a possible precursor of endometrial carcinoma.[1] The incidence of estrogen-associated endometrial hyperplasia and endometrial cancer was assessed in two large, long-term, randomized clinical trials. The histological results of the clinical studies indicate that the addition of PROVERA to an estrogen replacement regimen for 12 to 14 days per cycle reduces the incidence of endometrial hyperplasia in women with intact uteri. The addition of a progestin to 0.625 mg conjugated estrogen has not been shown to interfere with the efficacy of 0.625 mg conjugated estrogen for its approved indications.[1-3]

A 3-year, double-blind, placebo-controlled study of nonhysterectomized, postmenopausal women between the ages of 45 and 64 years were randomized to receive placebo, conjugated estrogen only, or conjugated estrogen plus cyclic PROVERA. The treatment group receiving 10 mg PROVERA plus 0.625 mg conjugated estrogens showed a significantly lower rate of hyperplasia in comparison to the group given 0.625 mg conjugated estrogens only. The 3-year histological results are summarized in Table 2.

Table 2. Number (%) of Endometrial Biopsy Changes Since Baseline After 3 Years of Treatment*

Histological Results	Placebo (n=119)	CEE† (n=119)	PROVERA‡ + CEE (n=118)
Normal/No hyperplasia (%)	116 (97)	45 (38)	112 (95)
Simple (cystic) hyperplasia (%)	1 (1)	33 (28)	4 (3)
Complex (adenomatous) hyperplasia (%)	1(1)	27(22)	2(2)
Atypia (%)	0	14(12)	0
Adenocarcinoma (%)	1 (1)	0	0

* Includes most extreme abnormal result
† CEE = conjugated equine estrogens 0.625 mg/day
‡ PROVERA = medroxyprogesterone acetate tablets 10 mg/day for 12 days

In a second study, postmenopausal women between the ages of 45 and 65 years were enrolled in a 1-year, double-blind study. All patients received conjugated estrogen 0.625 mg every day of a 28-day cycle, and were randomized to receive cyclic MPA 5 mg, cyclic MPA 10 mg, or conjugated estrogen only. The treatment groups receiving MPA 5 or 10 mg plus conjugated estrogens showed a significantly lower rate of hyperplasia in comparison to the group given conjugated estrogens only. The incidence of endometrial hyperplasia is shown in Table 3.

Table 3. Number (%) of Women with Endometrial Hyperplasia at 1 Year

	CEE*	MPA† + CEE*	
	(n=283)	MPA 5 mg (n=277)	MPA 10 mg (n=272)
Cystic hyperplasia (%)	55 (19)	3 (1)	0
Adenomatous hyperplasia without atypia	2(1)	0	0

* CEE = conjugated equine estrogen 0.625 mg every day of a 28-day cycle.
† Cyclic medroxyprogesterone acetate on days 15 to 28

INDICATIONS AND USAGE

PROVERA Tablets are indicated for secondary amenorrhea and for abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer. PROVERA Tablets are also indicated to reduce the incidence of endometrial hyperplasia in nonhysterectomized postmenopausal women receiving 0.625 mg conjugated estrogen.

CONTRAINDICATIONS

1. Thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions.
2. Liver dysfunction or disease.
3. Known or suspected malignancy of breast or genital organs.
4. Undiagnosed vaginal bleeding.
5. Missed abortion.
6. As a diagnostic test for pregnancy.
7. Known sensitivity to PROVERA Tablets.
8. Known or suspected pregnancy.

WARNINGS

1. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

2. Beagle dogs treated with medroxyprogesterone acetate developed mammary nodules some of which were malignant. Although nodules occasionally appeared in control animals, they were intermittent in nature, whereas the nodules in the drug-treated animals were larger, more numerous, persistent, and there were some breast malignancies with metastases. Their significance with respect to humans has not been established.

3. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

4. Detectable amounts of progestin have been identified in the milk of mothers receiving the drug. The effect of this on the nursing neonate and infant has not been determined.

5. Usage in pregnancy is contraindicated.

6. Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and

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cerebral thrombosis and embolism and the use of oral contraceptives.[4-7] The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[6] was about sevenfold, while Sartwell and associates[7] in the United States found a relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers. The American study also indicated that the risk did not persist after discontinuation of administration, and that it was not enhanced by long continued administration. The American study was not designed to evaluate a difference between products.

PRECAUTIONS

General

1. The pretreatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear.
2. Because progestogens may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.
3. In cases of breakthrough bleeding, as in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.
4. Patients who have a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.
5. Any possible influence of prolonged progestin therapy on pituitary, ovarian, adrenal, hepatic or uterine functions awaits further study.
6. Diabetic patients should be carefully observed while receiving progestin therapy.
7. The age of the patient constitutes no absolute limiting factor although treatment with progestins may mask the onset of the climacteric.
8. The pathologist should be advised of progestin therapy when relevant specimens are submitted.
9. Because of the occurrence of thrombotic disorders, (thrombophlebitis, pulmonary embolism, retinal thrombosis, and cerebrovascular disorders) in patients taking estrogen-progestin combinations and since the mechanism is obscure, the physician should be alert to the earliest manifestation of these disorders.

Carcinogenesis, Mutagenesis, Impairment of Fertility.

Long-term intramuscular administration of PROVERA has been shown to produce mammary tumors in beagle dogs. There was no evidence of a carcinogenic effect associated with the oral administration of PROVERA to rats and mice. Medroxyprogesterone acetate was not mutagenic in a battery of *in vitro* or *in vivo* genetic toxicity assays.

Medroxyprogesterone acetate at high doses is an antifertility drug and high doses would be expected to impair fertility until the cessation of treatment.

Information for the Patient

See Patient Information at end of insert.

Pregnancy

Pregnancy Category X--PROVERA Tablets are contraindicated during pregnancy. Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias in male fetuses may be doubled with exposure to these drugs. Some progestational drugs induce mild virilization of the external genitalia of female fetuses.

Nursing Mothers

The administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. Detectable amounts of progestin have been identified in the milk of nursing mothers receiving progestins. The effect of this on the nursing infant has not been determined.

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Pediatric Use

The safety and effectiveness of PROVERA Tablets in pediatric patients has not been established.

ADVERSE REACTIONS

Breast--Breast tenderness or galactorrhea has been reported.

Skin--Sensitivity reactions consisting of urticaria, pruritus, edema and generalized rash have occurred. Acne, alopecia and hirsutism have been reported.

Thromboembolic Phenomena--Thromboembolic phenomena including thrombophlebitis and pulmonary embolism have been reported.

Other--The following adverse reactions have been observed in women taking progestins, including PROVERA Tablets:

- breakthrough bleeding
- spotting
- change in menstrual flow
- amenorrhea
- edema
- change in weight (increase or decrease)
- changes in cervical erosion and cervical secretions
- cholestatic jaundice
- anaphylactoid reactions and anaphylaxis
- rash (allergic) with and without pruritus
- mental depression
- pyrexia
- insomnia
- nausea
- somnolence

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions:

- neuro-ocular lesions, eg, retinal thrombosis and optic neuritis.

The following adverse reactions have been observed in patients receiving estrogen-progestin combination drugs:

- rise in blood pressure in susceptible individuals
- premenstrual-like syndrome
- changes in libido
- changes in appetite
- cystitis-like syndrome
- headache
- nervousness
- fatigue
- backache
- hirsutism
- loss of scalp hair
- erythema multiforme
- erythema nodosum
- hemorrhagic eruption
- itching
- dizziness

Laboratory Tests--The following laboratory results may be altered by the use of estrogen-progestin combination drugs:

- Increased sulfobromophthalein retention and other hepatic function tests.
- Coagulation tests: increase in prothrombin factors VII, VIII, IX and X.
- Metyrapone test.
- Pregnanediol determination.
- Thyroid function: increase in PBI, and butanol extractable protein bound iodine and decrease in T3 uptake values.

DOSAGE AND ADMINISTRATION

Secondary Amenorrhea-PROVERA Tablets may be given in dosages of 5 or 10 mg daily for 5 to 10 days. A dose for inducing an optimum secretory transformation of an endometrium that has been adequately primed with either endogenous or exogenous estrogen is 10 mg of PROVERA daily for 10 days. In cases of secondary amenorrhea, therapy may be started at any time. Progestin withdrawal bleeding usually occurs within three to seven days after discontinuing PROVERA therapy.

Abnormal Uterine Bleeding Due to Hormonal Imbalance in the Absence of Organic Pathology- Beginning on the calculated 16th or 21st day of the menstrual cycle, 5 or 10 mg of medroxyprogesterone acetate may be given daily for 5 to 10 days. To produce an optimum secretory transformation of an endometrium that has been adequately primed with either endogenous or exogenous estrogen, 10 mg of medroxyprogesterone acetate daily for 10 days beginning on the 16th day of the cycle is suggested. Progestin withdrawal

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bleeding usually occurs within three to seven days after discontinuing therapy with PROVERA. Patients with a past history of recurrent episodes of abnormal uterine bleeding may benefit from planned menstrual cycling with PROVERA.

Reduction of endometrial hyperplasia in postmenopausal women receiving 0.625 mg conjugated estrogens- PROVERA Tablets may be given in dosages of 5 or 10 mg daily for 12 to 14 consecutive days per month, either beginning on the 1st day of the cycle or the 16th day of the cycle.

HOW SUPPLIED

PROVERA Tablets are available in the following strengths and package sizes:

2.5 **mg** (scored, round, orange)		
Bottles of 30	NDC	0009-0064-06
Bottles of 100	NDC	0009-0064-04
5 **mg** (scored, hexagonal, white)		
Bottles of 30	NDC	0009-0286-32
Bottles of 100	NDC	0009-0286-03
10 mg (scored, round, white)		
Bottles of 30	NDC	0009-0050-09
Bottles of 100	NDC	0009-0050-02
Bottles of 500	NDC	0009-0050-l 1

Store at controlled room temperature 20 to 25°C (68 to 77°F) [see USP].

REFERENCES

1. Writing Group for the PEPI Trial: Effects of hormone replacement therapy on endometrial histology in postmenopausal women. JAMA 275:370-375, 1996.
2. Woodruff JD, Pickar JH: Incidence of endometrial hyperplasia in postmenopausal women taking conjugated estrogens (Premarin) with medroxyprogesterone acetate or conjugated estrogens alone (The Menopause Study Group). Am J Obstet Gynecol 170: 1213-l 223, 1994.
3. Speroff L, Rowan J, Symons J, et al: The comparative effect on bone density, endometrium, and lipids of continuous hormones as replacement therapy (CHART Study) JAMA 276:1397-l 403, 1996.
4. Royal College of General Practitioners: Oral contraception and thromboembolic disease. J Coll Gen Pract **13:267-279,** 1967.
5. Inman WHW, Vessey MP: Investigation of deaths from pulmonary, coronary, and cerebral thrombosis and embolism in women of child-bearing age. Br Med J 2:193-l 99, 1968.
6. Vessey MP, Doll R: Investigation of relation between use of oral contraceptives and thromboembolic disease. A further report. Br Med J 2:651-657, 1969.
7. Sartwell PE, Masi AT, Arthes FG, et al: Thromboembolism and oral contraceptives: An epidemiological case-control study. Am J Epidemiol 90:365-380, 1969.

The text of the patient insert for progesterone and progesterone-like drugs is set forth below.

PATIENT INFORMATION

PROVERA Tablets contain medroxyprogesterone acetate, a progesterone. The information below is that which the U.S. Food and Drug Administration requires be provided for all patients taking progesterones. The information below relates only to the risk to the unborn child associated with use of progesterone during pregnancy. For further information on the use, side effects and other risks associated with this product, ask your doctor.

WARNING FOR WOMEN

Progesterone or progesterone-like drugs have been used to prevent miscarriage in the first few months of pregnancy. No adequate evidence is available to show that they are effective for this purpose. Furthermore, most cases of early miscarriage are due to causes which could not be helped by these drugs.

There is an increased risk of minor birth defects in children whose mothers take this drug during the first 4

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months of pregnancy. Several reports suggest an association between mothers who take these drugs in the first trimester of pregnancy and genital abnormalities in male and female babies. The risk to the male baby is the possibility of being born with a condition in which the opening of the penis is on the underside rather than the tip of the penis (hypospadias). Hypospadias occurs in about 5 to 8 per 1,000 male births and is about doubled with exposure to these drugs. There is not enough information to quantify the risk to exposed female fetuses, but enlargement of the clitoris and fusion of the labia may occur, although rarely.

(continued below)

Therefore, since drugs of this type may induce mild masculinization of the external genitalia of the female fetus, as well as hypospadias in the male fetus, it is wise to avoid using the drug during the first trimester of pregnancy.

These drugs have been used as a test for pregnancy but such use is no longer considered safe because of possible damage to a developing baby. Also, more rapid methods for testing for pregnancy are now available.

If you take PROVERA and later find you were pregnant when you took it, be sure to discuss this with your doctor as soon as possible.

℞ only

Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA

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